Remarks/Arguments

Claims 1-4, 6, 7, 15, 17-19, and 23 are presently pending. Claims 1 and 4 have been amended. Claims 2, 15, 17-19, and 23 have been cancelled without prejudice or disclaimer solely in order to expedite prosecution. *No new matter has been added.*

Moreover, amendment and/or cancellation of the claims during pendency of the application are not to be construed as acquiescence to any of the objections/rejections set forth in any Office Action, and were done solely to expedite prosecution of the application. Applicants submit that claims were not added or amended during prosecution of the instant application for reasons related to patentability. Applicants reserve the right to pursue the claims as originally filed, subsequently amended or added, or similar claims, in this or one or more subsequent applications.

35 USC §103

Rejection of Claims 1-4, 6, 7, 15, 17-19, and 23 under 35 USC §103(a)

The Examiner has rejected claims 1-4, 6, 7, 15, 17-19, and 23 under 35 USC §103(a) as being unpatentable over Fujimura et al., Salani et al. and Bradbury et al. The Office Action, on pages 5-8, highlights the disclosures of Fujimura et al., Salani et al. and Bradbury et al., and argues that such disclosures together make obvious the claims of the instant invention.

Applicants respectfully disagree and traverse this rejection. However, Applicants have amended the claims solely to expedite prosecution. In particular, Applicants have amended claims 1 and 4 to limit the endothelin receptor antagonist to *N*-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide (ZD4054). Support for these amendments may be found in the claims as originally filed.

Applicants assert that the Examiner has not met the appropriate burden to establish a *prima facie* case for obviousness, particularly for the claims as amended. In this regard, with respect to the combination of the teachings of Fujimura et al., Salani et al. and Bradbury et al, Applicants posit the question: what would motivate the ordinarily skilled artisan to combine these references? Applicants respectfully assert that Bradbury et al. is only one patent application out of a multitude of prior art that discloses endothelin antagonists. In order to arrive at the teaching of the present invention the ordinarily skilled artisan would have to:

1) select Bradbury et al. from all the prior art on endothelin antagonists; **then**

2) select Compound **(I)** from the 70 Examples in Bradbury et al. when there is nothing in Bradbury that particularly highlights this compound as being of interest; **then**

3) select the two particular references of Fujimura et al. and Salani et al. from the vast array of prior art on endothelin antagonists; **and then**

4) decide to combine the teaching of Bradbury et al. with the teachings of *both* of these references.

In this regard, Applicants assert that the ordinarily skilled person would not take these steps; and even if the ordinarily skilled person did take these steps, the ordinarily skilled person would have no reasonable expectation of success. It is only with the benefit of hindsight that the Examiner can make this allegation; and such hindsight, again, is impermissible. In fact, there is nothing in any of the cited references that would guide the ordinarily skilled artisan to particularly select the other two references and combine them in such a way to arrive at the present invention.

Furthermore, Applicants respectfully assert that the role of endothelin-1 (ET-1) in cancer is not as simplistic as the story laid out in the Office Action. Endothelin antagonists act by inhibiting the binding of ET-1 at its receptors. **There are two receptors – ET_A and ET_B**. More importantly, there is emerging evidence that the ET_B receptor is involved in apoptotic signalling, and that ET-1 acting at the ET_B receptor may actually provide a beneficial pathway in oncology by regulating apoptosis and by clearing excess ET-1. In this regard, we remind the Examiner that apoptosis is a natural process of self-destruction in certain cells, i.e., programmed cell death. It would, therefore, obviously be an undesirable property of an oncology compound to interfere or stop the process of apoptosis.

In fact, it is the inhibition of ET-1 acting at the ET_A receptor that has been considered an important mode of action in the management of certain cancers. The blocking of pro-apoptotic pathways would be undesirable in the treatment of cancer; hence a compound that specifically targeted the ET_A receptor while leaving the ET_B receptor unaffected would be of the greatest utility in the treatment of cancer. ZD4054 is such a compound.

The Examiners attention is further drawn to the enclosed article (cited in the co-filed SB/08 Form) from *Nature Reviews Urology* **6**, 350 (July 2009) entitled "Prostate cancer: New

endothelin-A receptor antagonist prolongs survival". This article discusses ZD4054 and the Phase II clinical trial results, and asserts that the compound has been "shown to improve the **overall survival** of men with hormone-resistant metastatic prostate cancer." (emphasis added) This article also contrasts ZD4054 with Atrasentan (ABT-627), another endothelin antagonist in clinical trials that has not shown the overall survival benefit:

> Atrasentan, another selective endothelin-A receptor antagonist, has a positive impact on PSA-based progression and markers of bone involvement. Failure of this drug to improve overall survival in a phase III trial may be due to the fact that it also inhibits signaling mediated by the endothelin-B receptor, which is thought to promote apoptosis and slow tumor spread. ZD4054 seems to have the advantage of not inhibiting endothelin-B receptor activity.

As such, and particularly in light of these findings, the fact that ZD4054 is such a suitable agent for use in treating cancer could not have been predicted from any of the prior art teachings, particularly when known selective endothelin A antagonists have measurable, undesirable, endothelin B properties.

Thus, not only would the ordinarily skilled person not have selected ZD4054 nor tested it in an ovarian model, from the cited prior art, the skilled person could not have predicted that ZD4054 would be such a suitable agent for this use.

Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1-4, 6, 7, 15, 17-19, and 23 under 35 USC §103(a), and favorable reconsideration.

Request for Phone Interview

Once the Examiner has had an opportunity to review the amendments and comments made herein, Applicants respectfully request a phone interview in order to discuss any final details that may help result in an allowance of the application with all pending claims.

CONCLUSION

Applicants respectfully request favorable reconsideration and allowance of all pending claims. Passage of the instant application to issuance is earnestly solicited. As noted above, if a telephone conversation with Applicants' attorney would help to expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at the telephone number below.

Applicants hereby request a one-month extension of time, and the Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No. 100864-1P US.

Respectfully submitted,

/Jacob G. Weintraub/

Name: Jacob G. Weintraub, Esq.
Attorney under 37 CFR 1.34
Dated: October 23, 2009
Reg. No.: 56,469
Phone No.: 781-839-4182
Global Intellectual Property, Patents,
AstraZeneca R&D Boston,
35, Gatehouse Drive,
Waltham, MA 02451